"Similarly, in the prior art, no descriptions have been given on estimating activation sequence within the brain by incorporating a three dimensional brain activation model into the inverse process. Innovation in the three dimensional brain imaging by using an activation model will advance state of the art in brain source imaging."

2.2 To provide proper antecedent basis for the claimed subject matter on "cellular action potentials, excitation rules, and inhomogeneity properties of brain" (claim 11) and "patch model of a biological system" (claim 9), the following paragraph has been added to the "Summary of the Invention" Section:

"This aspect of the invention further relates to using of heart-source model in which a priori information regarding physiological and pathophysiological processes is incorporated into by means of cellular automaton models with cellular action potentials being determined, excitation rules governing the activation within the heart, and inhomogeneity and anisotropy properties of the heart-torso tissues are taken into consideration in the heart and torso computer model. This aspect of the invention further relates to the heart source model in which cellular action potentials are determined by solving differential equations of a membrane patch, including variables of transmembrane ionic currents."

Re: Claim Objections

3. Claim 11 has been rewritten as follows to remove the informalities:

"The method of claim **5** wherein the electrical source model is constructed in such a way that *a priori* knowledge on the properties of brain physiological and pathological excitation processes are incorporated, including properties of neuronal cellular action potentials, excitation rules of the neural electrical activity, and inhomogeneity properties of the brain tissue."

Re: Claim Rejections – 35 USC 112

4. We have amended the application to clarify the distinctions of the present invention. Details follow.

5. We have made the following corrections:

(a) Claim 1 – We have deleted the indefinite term "*using different procedures*". Furthermore, we have added "or over a part of a surface out of the system" to clause (a) of Claim 1.

(b) Claim 13 - As suggested by the examiner, we have deleted "*three dimension space of the*" in line 6, added "three dimensional" prior to "biological system" in line 1. Furthermore, we have added "or over a part of a surface out of the system" in line 3 of Claim 13.

(c) Claim 13 – We have deleted "*over the cross-sections of the system, together with other imaging results on the biological system using different procedures such as magnetic resonance imaging and computer tomography*" in the end of Claim 13.

(d) Claim 18 – We have eliminated Claim 18 in the original application.

Re: Claim Rejections – 35 USC 101

7-8. We have eliminated Claim 18 in the original application.

Re: Allowable Subject Matter

9. We have amended, as described above, Claim 1-17 to overcome the rejections under 35 USC 112, second paragraph, set forth in this Office Action. Furthermore, we have amended Claim 9 to make the claim more clear as follows:

"The method of claim **3** wherein the electrical source model is constructed in such a way that *a priori* knowledge on the properties of physiological excitation processes are incorporated, including cellular action potentials, excitation rules that determine when and whether an excitable cell is to be activated as responding to the inputs from the adjacent excitable cells, models of the excitable membrane as described by differential equations, and inhomogeneity of a biological system."

Re: Conclusion

10. We have amended the prior art section of the application to further clarify that the present invention represents, to our knowledge, the first invention to image distributed electrical source distribution within the three-dimensional volume of the heart, the first invention to image excitation sequence within the three-dimensional volume of the heart, and the first invention to image excitation sequence within the three-dimensional volume of the brain. The amendments we have made in the Background of the Invention Section are summarized as follows:

On page 2, line 4, we have added "However, Savard et al.'s approach did not provide a means of imaging distributed cardiac electrical activity but a single equivalent dipole." to clarify the difference between this prior art and the present invention.

On page 2, line 8, we have added "However, Mirvis et al.'s approach also did not provide a means of imaging distributed cardiac electrical activity but only two discrete point sources within the heart." to clarify the difference between this prior art and the present invention.

On page 2, we have deleted "*Gulrajani et al. has reviewed efforts to localize cardiac electrical activity using one or two moving dipoles, see "Moving dipole inverse ECG and EEG solutions," IEEE Transactions on Biomedical Engineering, 903, 1984.*" since this publication is a review article.

On page 2, line 14, we have added "However, Barr et al.'s approach provided electrical potential distribution over the two dimensional surface of the epicardium." to clarify the difference between this prior art and the present invention.

On page 2, line 19, we have added "While Oster et al.'s approach provided activation sequence over the two dimensional surface of the epicardium, it did not provide a means of imaging cardiac activation sequence within the three dimensional volume of the heart." to clarify the difference between this prior art and the present invention.

On page 2, line 21, we have cited US patent 5,687,737 by adding "Branham et al. described a system of mapping activation sequence over the epicardial and endocardial surfaces, see U.S. patent 5,687,737. However, these heart surface activation imaging approaches only provided activation sequence over the heart surface, not within the three dimensional volume of the myocardium."

On page 3, line 15, we have cited US patent 6,240,307 by adding "Beatty et al. described a system mapping electrical activity of the heart from endocardial surface, see U.S. Patent 6,240,307."

On page 3, line 17, we have added "However, these approaches are invasive techniques, and the estimated electrical potential or activation patterns are over the two dimensional surface of endocardium, not within the three dimensional volume of the heart." to replace the original description of "*These approaches have been shown to be able to provide useful information in mapping endocardial activation in both ventricles and atria. However, all these endocardial-based techniques are invasive techniques and each presents with significant limitations.*"

On page 4, line 22, we have added "However, there has been no, to our knowledge, prior art in estimating excitation sequence of neuronal activation within the three-

dimensional volume of the brain." to clarify the difference between the prior art and the present invention.

On page 5, line 1, we have cited 4 relative US patents to further clarify the distinctive natures of the present invention as compared with prior art on brain source localization. The following has been added: "Amir et al. described a method and means of estimating brain source generators using a lead-field analysis method in a boundary element model of the head, see U.S. patent 5,701,909. However, Amir et al. did not show estimating three dimensional activation sequence within the brain. Tucker et al. also described a device of estimating brain electrical source, see U.S. patent 6,330,470. However, Tucker et al. also did not describe estimation of three dimensional activation sequence within the brain. Jewett et al. showed a device for measuring variations in measured physical parameters of source-generators, see U.S. patent 5,687,724. However, Jewett et al. also did not determine the activation sequence within the brain. Van Veen et al. described a method of estimating brain electrical sources by filter banks, see U.S. patent 5,263,488. However, Van Veen et al. also did not show estimating activation sequence within the brain."

On page 5, line 12, this paragraph has been substantially amended as follows: "To our knowledge, there have been no comprehensive reports to estimate the three-dimensional excitation sequence, three dimensional distribution of electrical source inside the heart from noninvasive electrocardiographic measurements made over the body surface or magnetocardiographic measurements made out of the body. There have been, to our knowledge, no comprehensive reports to estimate the activation sequence within the three dimensional volume of the brain from the electrical signals measured over the surface of the head or magnetoencephalograms measured out of the head. Lu et al attempted to localize the site of preexcitation of WPW syndrome using a model based inverse procedure, see "Extraction of implicit information in biosignals,"

published in Methods of Information in Medicine, 332, 1997. However, Lu et al. did not show determining the three dimensional activation sequence throughout the myocardial volume, did not show determining the three dimensional distribution of transmembrane potentials or electrical potentials within the myocardial volume, did not show determining the three dimensional distribution of current dipole or monopole sources within the myocardial volume."

On page 6, line 3, we have amended this paragraph to clarify the difference between the prior art and the present invention on heart imaging as follows: "However, in the prior art, no descriptions have been given on imaging cardiac electric source distribution within the three dimensional space of the heart using weighted minimum norm approaches. No descriptions have been given to estimate and image the activation patterns in the three dimensional myocardium. Further innovation in the three-dimensional cardiac electrical source imaging and in three-dimensional cardiac activation imaging is much needed."

On page 6, line 9, we have added this paragraph on the prior art of brain imaging as follows: "Similarly, in the prior art, no descriptions have been given on estimating activation sequence within the brain by incorporating a three dimensional brain activation model into the inverse process. Innovation in the three dimensional brain imaging by using an activation model will advance state of the art in brain source imaging."

Amendment of "Summary of the Invention" and "Abstract"

11. Based on the prior art as further clarified in the above, we have amended the "Summary of the Invention" section and "Abstract" section as follows:

On page 6, line 17, "*and*" has been amended to "and/or".

On page 6, line 23, "*activation patterns and electrical source distribution*" has been amended to "electrical sources and/or activation patterns".

On page 7, line 2, "*activation patterns and electrical source distribution*" has been amended to "electrical sources and/or activation patterns".

On page 7, line 5, "*activation patterns and source distribution*" has been amended to "activation patterns and/or source distribution".

On page 7, line 8, "*activation patterns and source distribution*" has been amended to "electrical sources and/or activation patterns".

On page 7, lines 15 and 17, "*activation patterns and electrical source distribution*" has been amended to "electrical sources and/or activation patterns".

On page 7, line 23, "*activation sequence and electrical source*" has been amended to "activation sequence and/or electrical source".

On page 8, line 6, "*activation sequence and electrical source*" has been amended to "activation sequence and/or electrical source".

On page 8, line 9, "*activation sequence and source distribution*" has been amended to "activation sequence and/or source distribution".

On page 9, lines 18 and 21, "*activation sequence and electrical source*" has been amended to "activation sequence and/or electrical source".

On page 9, line 23, "activation *sequence and source distribution*" has been amended to "activation sequence and/or source distribution".

On page 10, line 6, "*activation sequence and/or source distribution*" has been amended to "activation sequence and/or source distribution within the heart by".

On page 10, line 8, "*and*" has been amended to "and/or".

On page 25, line 10, "excitation sequence and electrical source" has been amended to "excitation sequence and/or electrical source".

On page 25, we have deleted "*, together with imaging results from other modalities including magnetic resonance imaging and computer tomography*" from the last sentence.

Added Claims 18-21

12. According to the clarified description of the present invention as established by the prior art, we request the following claims (18-21) be allowed, which accurately reflect the invention as made under the support of US Government:

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18. A method of imaging of electrical activities in a heart within a body comprising the steps of:

(a) collecting signals over a part of a surface of the body or over a part of a surface out of the body using a plurality of sensors and a data acquisition unit,

(b) determining positions of the sensors,

(c) determining geometry information of the body,

(d) constructing an electrical source model of the heart, which comprises a three dimension distribution of current dipoles or monopoles or electric potentials, or a computer heart model incorporating physiological a priori information that simulates the physiological and pathophysiological processes of the heart;

(e) estimating activation patterns of the electrical activity within the three dimension space of the heart, by comparing and minimizing the difference between the collected signals and source model generated signals over the same sensor positions and over a certain time epoch, and

(f) displaying the estimated activation patterns within the three dimension of the heart.

19. An apparatus for imaging of electrical activities of a heart within a body, comprising a plurality of sensors for detecting signals over a part of a surface of

the body or over a part of a surface out of the body, means for collecting the detected signals, means for determining positions of the sensors, means for determining geometry information of the body, means for constructing an electrical source model of the system, means for estimating activation patterns within the three dimension volume of the system, by comparing and minimizing the difference between the detected signals and source model generated signals over the same sensor positions over a certain time epoch, and means for displaying the estimated activation patterns within the three dimension space of the heart.

20. A method of imaging of electrical activities in a heart within a body comprising the steps of:

(a) collecting signals over a part of a surface of the body or over a part of a surface out of the body using a plurality of sensors and a data acquisition unit,

(g) determining positions of the sensors,

(h) determining geometry information of the body,

(i) constructing an electrical source model of the heart, which comprises a three dimension distribution of current dipoles or monopoles or electric potentials, or a computer heart model incorporating physiological a priori information that simulates the physiological and pathophysiological processes of the heart;

(j) estimating electrical source distributions within the three dimension volume of the heart, by comparing and minimizing the difference between the collected signals and source model generated signals over the same sensor positions and over a certain time epoch, and

(k) displaying the estimated electrical source distributions within the three dimension space of the heart.

21. An apparatus for imaging of electrical activities in a heart within a body, comprising a plurality of sensors for detecting signals over a part of a surface of the body or over a part of a surface out of the body, means for collecting the detected signals, means for determining positions of the sensors, means for determining geometry information of the body, means for constructing an electrical source model of the heart, means for estimating electrical source distributions within the three dimension volume of the heart, by comparing and minimizing the difference between the detected signals and source model generated signals over the same sensor positions over a certain time epoch, and means for displaying the estimated electrical source distributions within the three dimension space of the heart.
